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Review Article

A REVIEW ON ISCHEMIC STROKE RISK FACTORS

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ABSTRACT

Stroke is a leading cause of morbidity and mortality all around the world, with up to 40% of survivors not expected to recover independence from severe disabilities. This equates to an immense financial burden on health systems worldwide.Stroke is a heterogeneous, multifactorial disease regulated by modifiable and nonmodifiable risk factors.Nonmodifiable risk factors serve as markers for high stroke risk, whereas modifiable risk factors are amenable to intervention for lower stroke risk. Modifiable factors include a history of high blood pressure, diabetes mellitus coronary heart disease, dyslipidemia and so forth. Nonmodifiable factors include age, sex and race. Other less-well documented risk factors include geographic location, socioeconomic status and alcoholism. Approximately 80% of stroke events could be reduced by making simple lifestyle modifications. This review article provides a comprehensive information on various modifiable and nonmodifiable risk factors of ischemic stroke.

Keywords: ischemic stroke, risk factor, modifiable , nonmodifiable

INTRODUCTION

At present stroke is considered as a major cause of mortality and morbidity across the globe[1]. It is the number one cause of death in China, the third most common cause of death in the United Kingdom[2] and the fourth leading cause of death in the United States[3, 4].Approximately, 17 million people suffered a stroke in 2010[5].A stroke also known as brain attack is the result when the blood supply to the part of the brain is interrupted. There are two main types of stroke: ischemic stroke which results due to lack of blood flow either thrombotic or embolic and hemorrhagic stroke which results due to bleeding into brain parenchyma. Ischemic stroke accounts for 85% of the total stroke[6].A transient ischemic attack (TIA) is a self-resolving focal cerebral ischemia with symptoms lasting <24 h without any evidence of acute brain tissue infarction[7].Approximately 15% of all strokes are heralded by a transient ischemic attack[8].Thrombotic strokes are the most common type of ischemic stroke which is a result of blood clot (thrombus) formation that blocks the blood flow to parts of the brain. A formation of thrombus in an artery is commonly precipitated by atherosclerosis. Embolic strokes occur when a piece of a clot (embolus) breaks and is carried by the bloodstream to the brain, where the larger arteries branch off into smaller vessels. The blood clot reaches a point where it can travel no further thereby plugging a small cerebral artery and cutting off the blood supply to the brain.

Risk factor assessment is an important step toward understanding the origin of a disease and in formulating a preventive strategy. A number of risk factors are associated with an increased risk of stroke. They can be stratified into modifiable and nonmodifiable risk factors. Modifiable risk factors include those resulting from lifestyle choices and the environment, and can be modified with the help of healthcare professionals, treatment and continuing education.Modifiable risk factors include, but are not limited to hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, smoking, and alcoholism[9].Unmodifiable risk factors encompass factors related to hereditary or natural processes and cannot be modified. Almost 80% of stroke events could be minimized if there is a change in lifestyle and dietary modification[10].

Modifiable risk factors:

Hypertension:

Hypertension is the most prominent modifiable risk factor for ischemic stroke, and it afflicts more than 75 million adults ≥20 years of age in the U.S. It is the most frequently identified risk factor in all subtypes of ischemic stroke[11-13].The relationship between BP and stroke risk is strong, continuous, consistent, independent, predictive, and etiologically significant. Hypertension being the most prevalent and modifiable risk factor for stroke increases with age and has a life time probability of 90% in those who survive to 80 years[14].Approximately quarter of the adult population and about half of the population aged 65 years and above, suffer from arterial hypertension.Although earlier studies have demonstrated that hypertension was more frequent in small vessels occlusion than large artery atherosclerosis[15, 16], however,

various studiesdid not find any significant difference in the prevalence of hypertension across ischemic stroke subtypes as mentioned above.

Diabetes mellitus:

Diabetes is a clear risk factor for stroke, particularly ischemic stroke. Disorders of glucose metabolism have a high prevalence in patients with cerebrovascular disease.People with diabetes have more than double the risk of ischemic stroke relative to individuals without diabetes[17]. Twenty-eight percent of patients with ischemic stroke have pre-diabetes while up to 45% of patients have overt diabetes. Diabetes mellitus has been reported to be more closely associated with small vessel disease than with other subtypes[18].Histological analysis of brain tissue following stroke have shown that endothelial proliferation and hyalinosis of small intraparenchymal vessels occur more frequently in diabetic patients than nondiabetic patients. It has further been suggested that diabetic individuals are more susceptible to irreversible than reversible ischemic damage and that hyperglycemia may induce early preprogrammed cell death[19].It is also apparent that diabetes and stroke risk is gender-dependent with the effect being more pronounced in the female population, and diabetes is considered a cardiovascular disease equivalent for stroke in women[20].

Smoking:

Smoking is associated with reduced blood vessel distensibility/compliance, elevated fibrinogen levels, increased platelet aggregation, decreased highdensity lipoprotein, cholesterol levels, and higher hematocrit. The relation between smoking and atherosclerosis was first reported in the early 20th century with a high occurrence of severe distal ischemia among male addicted smokers[21].The Framingham Heart Study was one of the first studies to assess the relationship between smoking and the type of stroke, including the number of cigarettes smoked, and the effect of stopping. Results concluded that the relative risk of stroke in heavy smokers (>40/day) was twice that of light smokers (<10/day), with the risk increasing with the number of cigarettes smoked. Smoking cessation lowered the relative risk to that of nonsmokers. The reduction in risk ratio was significant by 2-years following cessation and reached the level of a nonsmoker at 5-year[22].

Coronary heart disease:

Individuals with a presence of coronary artery disease have double the risk of stroke compared to patients without coronary artery disease. The attributable risk of stroke due to coronary artery disease is approximately 12%. Atherosclerosis is a chronic inflammatory disease of the arteries, in large part due to the deposition of lipoproteins (plasma proteins that carry cholesterol and triglycerides). Aortic atheroma >4 mm is an independent risk factor for new and recurrent stroke[23]. The risk of stroke and cerebral infarction have been shown to gradually increase with increasing numbers of carotid plaques and when adjusted for cardiovascular risk factors. The risk of stroke in subjects with severe plaques was 24-fold increased and the risk of cerebral infarction almost tripled compared with subjects without plaques.

Atrial fibrillation:

Atrial fibrillation (AF) is a leading cause of morbidity and mortality with 5 million incident cases a year and an increasing prevalence worldwide[24].AF is a strong, independent and one of the most important risk factor for ischemic stroke as patients with AF are 5 times more likely to experience a stroke event than those without AF[25]. One in every six strokes occurs in a patient with AF, and about 10% of all ischemic strokes are caused by embolism of left atrial appendage thrombi[26]. Study has indicated that ischemic stroke occurring with AF is almost twice as likely to be fatal than stroke not associated with AF, recurrence was more frequent and functional deficits were more severe in survivors[27].Outpatient continuous arrhythmia monitoring is widely increasingly showing that AF may actually be responsible for a higher percentage of unexplained strokes than was previously known.

Left ventricular hypertrophy:

Increased left ventricular (LV) mass is a risk factor for cardiovascular diseases and is independent of other cardiovascular risk factors including arterial hypertension. LVH is also independently associated with risk of ischemic stroke. In hypertensive patients, concentric and eccentric hypertrophy was associated with a 2-fold increase in stroke incidence, but concentric remodeling did not carry increased risk. An increased risk of thromboembolic events has been associated with low left ventricular ejection fraction(LVEF) , particularly with severely decreased LVEF , but only in women[28].

Dyslipidemia:

Abnormalities in several serum lipid indices have been linked to symptomatic vascular disease. Dyslipidemia represents one of the major risk factors for atherosclerosis affecting the arteries of large and medium caliber and consequently causing ischemia in the brain[29]. Elevated low-density lipoprotein cholesterol and triglyceride levels are significant risk factors in patients with atherothrombotic cerebrovascular disease presenting as stroke or transient ischemic attack. Hyperlipidemia history increases the incidence of stroke.Hypercholesterolemia is a recognized risk factor for stroke due to large artery atherosclerosis[30]. Hyperlipidemia accelerates damages on a certain cerebral artery and makes atherosclerosis symptomatic.

CRP:

Several large epidemiological studies have consistently found higher circulating levels of CRP using a high-sensitivity assay (commonly referred to as highsensitivity CRP, or hsCRP) to be associated with an increased risk of vascular events independent of traditional vascular risk factors[31]. It is an acute-phase protein produced by the liver, and the serum levels of this protein increase in response to tissue injury, infection, inflammation and neoplastic proliferation.CRP has been demonstrated to predict disease progression and clinical adverse events in coronary, cerebrovascular, and peripheral circulation in apparently healthy subjects as well as in patients with prevalent atherosclerosis. The serum high-sensitivity C reactive protein (hs-CRP) level is known to be a predictive marker of the degree of atherosclerosis and future cardio

and cerebrovascular events[32].

Homocysteine:

Homocysteine is a homologue of the naturally occurring amino acid cysteine and permanently degrades cysteine and lysine amino acid residues in proteins, gradually affecting function and structure. Over the last 10 years evidence has accumulated that elevated plasma or serum concentrations of the sulphur amino acid homocysteine are associated with an increased risk of atherosclerosis, cardiovascular disease and ischemic stroke[33].A case-control study conducted by Eikelboom et al. in 219 patients with a firstever ischemic stroke and 205 control subjects stratified by age, sex and postal code revealed that increasing homocysteine was a strong and independent risk factor for ischemic stroke[34].

Fibrinogen:

Fibrinogen is a major coagulation protein and involved in platelet aggregation and inflammation[35].Various studieshave shown that hyperfibrinogenemia is a strong and independent risk factor for stroke including a study on 792 men by Wilhemsen et al. which revealed that there were 37 patients with incident stroke after 13.5 years follow up, and high serum fibrinogen level was significantly associated with an increased risk of stroke[36, 37]. It has been suggested that increased viscosity and higher available substrate quantity resulting from elevated plasma fibrinogen concentration may promote coagulation and act as a risk for small-vessel thrombotic occlusion, thus affecting the phenotype of the cerebral infarction[38].A case-control study including 105 ischemic stroke patients and 352 controls indicated that the risk of stroke was 1.78-fold in patients with fibrinogen concentrations greater than 3.6g/L[39].

Hematocrit:

Hematocrit is the ratio of the volume occupied by red blood cells to the volume of the whole blood. Hematocrit plays a crucial role in cerebral blood flow (CBF) dynamics and is a major determinant of the nature of the blood flowing through the vascular system. It is the major determining factor of whole blood viscosity[40].Elevated hematocrit leads to blood viscosity and has an adverse effect in acute stroke and also found to be a potential determinant of infarct growth[41].Higher hematocrit levels have previously been associated with increased stroke risk, especially hematocrits >45%[42, 43].Some studies has established that high hematocrit values being a risk factor for cerebral infarction are essential when arteries are of small caliber or severely stenosed by atherosclerotic changes[44].

Risk factors	Frequency	%
Hypertension	268	78.1%
Diabetes	215	62.7
Hyperlipidemia	188	54.8
Coronary artery disease	83	24.2
Atrial fibrillation	45	13.1
Past history of stroke	35	10.2
Smoking	25	7.2

Frequency and percentage of different risk factors for all stroke[15]

Risk factor	SVO	CE n%	LAA	Undetermined	P-value
Hypertension	93(84.0)	60(80.0)	39(78)	69(75.0)	0.007
Diabetes	86(78.1)	47(62.4)	30(60)	50(54.9)	0.000
Hyperlipidemia	67(61.9)	36(48.0)	27(54)	52(56.5)	0.600
Ischemic heart Disease	17(15.4)	40(53.3)	10(20)	15(16.3)	0.000
History of stroke	8(7.2)	13(17.3)	6(12)	6(6.5)	0.49

Distribution of risk factors among major categories of stroke[15]

SVO – Small Vessel Occlusion, CE – Cardio Embolic, LAA – Large Artery Atherosclerosis

Non modifiable risk factors:

Age:

One of the most significant stroke risk factors is advanced age with 95% of strokes occurring in people age 45-years and above, and two-thirds of strokes occurring in those over the age of 65. Mortality risk also increases with age. However stroke can occur at any age[45].Stroke etiology is much more varied in younger stroke cohorts and frequencies of etiological subtypes also differ in frequency between different ethnic populations.

Sex:

Men have a slightly greater risk of stroke, particularly in middle to old age. Neverthelessthis excess risk among men is not present in the very elderly or the young. Overall, men have about a 19% greater chance of a stroke than women. Among people under age 65, the risk for men is even greater when compared with that of women[46].Women had a lower age adjusted risk of ischemic stroke than men at ages 65 years but women had a higher risk than men at ages.

Race:

The incidence and standardised mortality ratios for stroke are known to vary between different ethnic groups and may reflect genetic or nongenetic differences. Individuals of black descent have been shown to have an excess burden of stroke compared with white. Hispanics and blacks had a significantly greater proportion of intracranial atherosclerotic stroke than whites and higher incidence rates. The proportions of lacunar, extracranial atherosclerotic and cryptogenic stroke were not significantly different among the three race-ethnic groups, but blacks (21%) and Hispanics (22%) had a slightly greater proportion of lacunar stroke then whites (16%)[47].

CONCLUSION

Various risk factor have been established in the occurrence as well as the severity of ischemic stroke. This risk factor is also significant in the determination of ischemic stroke subtype. A plethora of research has been conducted over the last decade to elucidate the association between ischemic stroke subtypes and the factors described above. Improving awareness in the general population regarding modification of life style, adapting healthy dietary habits, and regular medical follow up for screening purposes in a younger age group may play an important pivotal role in reducing the disease burden caused by stroke.

Abbreviations:

AF: Atrial fibrillation

TIA: Transient ischemic attack

SVO: Small vessel occlusion

CE: Cardio embolic

LAA: Large artery atherosclerosis

LVEF: Low left ventricular ejection fraction

Conflict of interest:

I declare no conflict of interest

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